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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/817,448	03/26/2001	H. Craig Dees	PHO-120	2388

7590 06/15/2004

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,448	DEES ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-34,36-40 and 46-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-34, 36-40, and 46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 3/22/04 is acknowledged and has been entered. Claims 1, 3-6, 11, 14, 16-24, 29, 31-34, 46, and 47 have been amended. Claims 7, 35, and 41-45 have been cancelled. Accordingly, claims 1-6, 8-34, 36-40, and 46-50 are pending and are under examination.

Rejections Withdrawn

2. The rejections of claims 7 and 35 are now moot in light of Applicant's cancellation of the claims.

3. In light of Applicant's amendment, the rejection of claim 11 under 35 U.S.C. 112, second paragraph, is hereby, withdrawn.

4. In light of Applicant's amendment, the rejection of claims 1-5, 8-33, 36-40 and 46-50 under 35 U.S.C. 112, first paragraph, is hereby, withdrawn.

5. In light of Applicant's submission of Terminal Disclaimer, the rejection of claims 22-28 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-33 of U.S. Patent No. 6,331,286, is hereby, withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 16-28 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-28 provide
Claim 16 provides for the use of a halogenated xanthene, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 16-28 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The claimed invention is drawn to a medicament or a pharmaceutical composition *comprising* halogenated xanthene as a primary active component, which is used in combination with ionizing radiation, for phototherapeutic treatment of human or animal tissue. Accordingly,

7. Claims 1, 3, 5, 8-12, 15-18, 20, 29, 31, 33, 36-39, 46-48, and 50 stand rejected under 35 U.S.C. 102(b) as being anticipated by Serafini et al. (Journal of Nuclear Medicine, 1975) for reasons of record.

8. Claims 1, 3, 5, 8-10, 12, 16, 18, 20, 29, 31, 33, 36-39, 46-48, and 50 stand rejected under 35 U.S.C. 102(b) as being anticipated by Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) for reasons of record.

9. Claims 1, 3-5, 16, 18, 19, 29, 31-33, 46, 47, and 50 stand rejected under 35 U.S.C. 102(b) as being anticipated by Fondren et al. (Environ Entomol (1978)) for reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 14 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Norman et al. (Invest Radiol, 26: S120-S121, 1991) for reasons of record.

11. Claims 2 and 30 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) or Fondren et al. (Environ Entomol (1978)) for reasons of record.

12. Claim 6, 13, 21, 34, 40, and 49 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) or Fondren et al. (Environ Entomol (1978)) in view of Khaw et al. (US 5,780,052) for reason of record.

Response to Arguments

13. Applicant's arguments filed 3/12/04 have been fully considered but they are not persuasive.

A) Applicant amended language of the claim so as to be limited to "consisting of a halogenated xanthene" and argues that Serafini fails to describe or suggest the medicaments of the claimed invention. Applicant submits that such amendment should overcome the rejection as being anticipated by Serafini.

In response, as recited in the pending claims, Serafini teaches a medicament or pharmaceutical composition consisting of a halogenated, i.e. iodinated, xanthene, in this case, Rose Bengal. Serafini teaches that the agent is for treating diseased tissue as a radiopharmaceutical agent. Specifically, Applicant has not shown that the halogenated xanthene which is Rose Bengal taught by Serafini as being radioactive, is structurally distinct from the Rose Bengal taught in the claimed invention.

Additionally, a recitation of the intended use of the claimed invention must result in a structural difference between the halogenated xanthene of the claimed invention and the halogenated xanthene of the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

B) Applicant amended language of the claim so as to be limited to "consisting of a halogenated xanthene" and argues that Neckers fails to describe or suggest the

medicaments of the claimed invention. Applicant submits that such amendment should overcome the rejection as being anticipated by Neckers.

In response, as recited in the pending claims, Neckers teaches a medicament or pharmaceutical composition consisting of a halogenated xanthene which is Rose Bengal or 2,4,5,7- tetraiodo-3', 4', 5', 6'- tetrachlorofluorescein. Neckers specifically teaches that Rose Bengal has selective concentration on selected tissues, i.e. tumor: its spectrum is most diagnostic of its immediate environment. Specifically, Applicant has not shown that the halogenated xanthene which is Rose Bengal taught by Neckers, is structurally distinct from the Rose Bengal taught in the claimed invention.

Additionally, a recitation of the intended use of the claimed invention must result in a structural difference between the halogenated xanthene of the claimed invention and the halogenated xanthene of the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

C) Applicant argues that the combination of the teachings of Neckers with the teachings of Norman is improper in rejecting claim 14 which applies "ionizing radiation ... at an energy of greater than approximately 1 KeV and less than approximately 1000 MeV, because while Neckers discussed halogenated xanthenes, there is no discussion

of this particular wavelength range. Applicant contends that the teachings of Norman provides discussion of this wavelength range in question but fails to apply it specifically on halogenated xanthenes; instead, its application is on gandolinium contrast media.

In response, the teaching of Norman in halogenated or iodinated contrast media, in this case gandolinium, is combined with the teaching of Neckers of halogenated or iodinated xanthenes or Rose Bengal which is known for its use as a contrast agent, because according to Norman, dose enhancement factor (DEF) in contrast media increases linearly with the concentration of halogen, i.e. iodine, in as far as wavelength range application is concerned. As an example in Figure 1, DEF is a function of the iodine concentration in a lymphocyte medium during irradiation at 140 keV. Accordingly, Applicant's argument of the distinction between gandolinuim and iodine is not on point. One of ordinary skill in the art at the time of the instant invention would have been motivated to activate the halogenated xanthene or Rose Bengal, taught by Neckers, with ionizing radiation at 140 keV as taught by Norman because Norman specifically taught that DEF is a function of the iodine concentration in a contrast medium when applying ionizing radiation at 140 kEV, and Rose Bengal as taught by Neckers, is an obvious variation of a rediosensitizing contrast agent upon which ionizing radiation can be applied for use in imaging, and which have been taught by Neckers as being characteristically capable of photodynamic and radiation activation.

D) Applicant argues that Rose Bengal was not known to have usefulness as contrast agent at the time of the instant invention; thus Norman would not be led to apply general knowledge of contrast media to halogenated xanthenes.

Contrary to Applicant's argument, Neckers which was combined with the teaching of Norman, teaches and describes that halogenated xanthene such as Rose Bengal have usefulness as contrast agent because of its properties: 1) as a photodynamic sensitizer, and 2) its capacity to be activated as an imaging agent, i.e. shows fluorescence.

E) Applicant argues that there is no disclosure in Fondren of a radiosensitizer medicament as recited in the rejected claims; thus, Fondren does not anticipate or render obvious the claimed invention. Applicant contends that they are not claiming the rights to Rose Bengal or any halogenated xanthene, but rather are claiming certain types of medicaments or pharmaceutical agents for radiosensitization that contain Rose Bengal or another halogenated xanthene as an active ingredient. Applicant argues that the agents in Fondren are not the same composition as the claimed invention, and that Fondren describes only properties of the halogenated xanthenes such as toxicity properties. Applicant also argues that Fondren does not describe or suggest medicaments or pharmaceutical agents for incorporeal use.

In response, as recited in the pending claims, Fondren teaches a composition consisting of a halogenated, i.e. iodinated, xanthene, in this case, Rose Bengal. Fondren et al. enumerate six halogenated xanthene dyes including

octabromofluorescein, erythrosin B, phloxin B, eosin Y, and tetrachlorofluorescein. Accordingly, Fondren anticipates the claimed invention. While Applicant reiterates that the medicament composition of the claimed invention, which contains halogenated xanthene is distinct from the halogenated xanthene or Rose Bengal as taught by Fondren, Applicant fails to recite and/or otherwise, describe how the claimed composition is structurally distinct as a medicament such as for example a modification of structure, inclusion of moieties, etc. Additionally, it is a general rule that merely discovering and claiming a new benefit (other than toxicity) of an old product cannot render the product again patentable. In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979).

In as far as the intracorporeal use halogenated xanthenes as medicaments, a recitation of the intended use of the claimed invention must result in a structural difference between the halogenated xanthene of the claimed invention and the halogenated xanthene of the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

F) Applicant argues that the combination of Serafini, Neckers, or Fondren with Khaw does not render obvious the claimed invention, specifically claims 6, 13, 21, 34, 40, and 49 because it fails to teach or suggest liposomal targeting of liposomal agents and gamma imaging. Applicant contends that their amendment of claims 6 and 34 omitted antibodies to thus obviate this rejection.

In response, claims 6 and 34 were amended to include "wherein said targeting moiety is selected from the group consisting of DNA, RNA, amino acids, proteins, ligands, ... protein receptors, ..." which does not appear to exclude the antibodies taught by Khaw as targeting moiety. In as far as gamma ray imaging for use with contrast agents in diagnostic purposes as opposed to therapeutic purposes, a recitation of the intended use of the claimed composition must result in a structural difference between the claimed composition and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). In this case, Khaw teaches enhancing effects of therapy that kills diseased (malignant/tumor) cells in vivo by providing (immuno)liposomes specific for an internal cellular antigen present in degenerating neoplastic cells. Techniques are known for liposome targeting such as conjugating antibodies to cell-surface (malignant) antigens to pharmacologically active agents and labels to permit diagnosis, localization, and

therapy toward tumors (see column 7, line 48 to column 8, line 3). Agents include radiosensitizing agents, cytotoxic agents, and radionuclides (see column 3, first paragraph and column 4, lines 18-27). Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to administer Rose Bengal taught by Serafini, Neckers, and Fondren using proteins and ligands as taught by Khaw because Khaw specifically taught that pharmaceutically or therapeutically activatable agents can be incorporated into immunoliposomes, for targeting delivery to specific tissue, ie. malignant tumors, which allows for localization of the agent into targeted specific tissues and Rose Bengal has been taught by Neckers to be activatable by radiation. Further, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute use of gamma imaging as taught by Khaw into the teachings of Serafini, Neckers, and Fondren because use of gamma radiation is an obvious variation of imaging technique which is routinely known in the art.

14. For reasons aforementioned, no claims are allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641

Gailene R. Gabel
Patent Examiner
Art Unit 1641
June 7, 2004